Herbal Medicine in the Treatment of Addictions

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Preface

Plants have been used for medicinal purposes throughout human history and although it may seem to us that modern life is innately much more stressful than long ago, the struggle for basic survival then must have been at least as worrying as the more 'sophisticated' concerns of today. Thus, it seems likely that healers in primitive societies probably had to treat exactly the same range of disorders as those with which we are familiar including, for example, psychoactive herb-related psychosis. Spells and incantations to drive away evil spirits, which some may interpret as early psychotherapy, might have been combined with the use of herbs with psychoactive properties. The side-effects of very powerful psychoactive plants were probably observed and treated with herbal remedies.

While modern medicines are firmly rooted in herbalism, they have undergone such profound changes that many people are uneasy about their use and are keen to return to the natural products. However, it is important to emphasise that 'natural' and 'traditional' medicines are not always benign and gentle, and can themselves cause serious side-effects. Unfortunately, the public and particularly vulnerable groups such as those with problems related to dependence on psychoactive substances are poorly safeguarded in this respect because, in most countries, the regulation and registration of herbal medicines is poorly developed and the quality of herbal products sold is generally not guaranteed.

This project has brought together, for the first time, experts from different parts of the world with specific interest, knowledge, and experience in the use of herbal medicine in the treatment of substance abuse and dependence. The report provides evidence and experienced-based knowledge on many aspects of the issues in the field. I am confident that it will be of immense value to academics, practitioners, service providers, policy makers and ultimately to those who suffer and rightly deserve evidence based and better regulated care-the patients.

Hamid Ghodse CBE (Hon)

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1.0 Background, Rationale for the Meeting

The use of herbal medicine goes back thousands of years. Although there have been sporadic claims about its use in the treatment of addictions, there has not yet been any specific evidence of effectiveness. With that in mind, an international expert group was convened to examine a range of issues.

This initiative aimed at bringing together a group of international experts to consider a number of areas of interest, including existing evidence, lessons learnt from herbal medicine in other health conditions, gaps in knowledge and opportunities for future development.

Experts attended from ten countries: Brazil, Finland, Germany, Mexico, India, Hungary, China, Ghana, Vietnam and the United Kingdom.

The group met in central London for a 4-day residential programme. In preparation for the programme, the international experts were asked to contribute a background paper for presentation to the group focusing on their particular area of expertise and/or knowledge.

Participants were encouraged to contribute and comment on a number of issues in relation to herbal substances in the treatment of addictions, including: efficacy, safety, usefulness, toxicity and side effects of the herbal substances.

2.0 Addiction Treatment: Present Status of Pharmacotherapy

Current goals for the pharmacotherapy of addiction include: preventing withdrawal symptoms, reducing drug craving, normalising the physiological functions affected by drug use, and targeting the treatment agent to the specific site of action or physiological system that is affected by the drug of abuse. Recent reviews of approved pharmacotherapies for the treatment of addictions demonstrate both a striking paucity of novel treatment agents and the modest efficacy of traditionally prescribed medication. The concept and technique of substitution has been extended from opiates to other addictive drugs (e.g. nicotine), but cost-effective medications for drugs such as cocaine and amphetamines are still lacking. Investment in original drug development tends to be either rare or exceptional and of modest scale. The principal reasons for reluctance to enter this market by drug companies include: disproportionately high development costs for an unsafe and controversial consumer market; modest emphasis on and input by governments into this area of expenditure; and frequent shifts in terms of clinical priorities.

3.0 A New Interest in Herbal Medicine

The popularity of herbal medicines for the treatment of various chronic conditions is steadily growing in virtually all industrialised countries. Much higher annual growth rates have been recorded over the last two decades for several significant medicinal plants compared to the pharmaceutical market in general. From this point of view, addiction treatment is no exception; recent population surveys indicate a growing popularity of alternative medicines among drug addicts seeking help or undergoing treatment. As a reaction to the disappointing long-term success rates of available medications and treatment modalities, a considerable proportion of drug users are seeking help from alternative treatment options, including herbal, complementary and alternative medicines (CAM). Several national and trans-national studies show that depression and anxiety are among those conditions for which people frequently seek help from CAM.

In a few regions of the world, only non-pharmacotherapeutic approaches are socially acceptable options for the local population. The reasons are complex and may include political, economic, socio-cultural, and/or religious factors. The cost of a long-term pharmacotherapy for the increasing numbers of alcohol, tobacco and other drug addictions are simply unaffordable for those individuals involved and for the society as a whole. In some countries, both social rules and tight regulations make many of the drugs used in treatment programmes in Western countries legally unavailable.

Experience gained in the few countries using herbal preparations for addiction treatment seems to indicate that such locally available and widely accepted treatment options may not only prove to be both medically and cost-effective but may also result in considerable cost-savings for health care systems in other countries with limited resources.

It may be postulated that the techniques and remedies used in traditional settings to 'treat' those who are under the influence of addictive psychoactive drugs are linked to those addictive substances which have long been used for recreational, ceremonial and other social purposes. The local 'remedies' used for such a purpose are generally 'antidotes' used for both ritual intoxication and acute emergency situations. Their wider applicability in allopathic medicine is still to be tested and validated.

The global spread of heroin, for example, has prompted experimentation with locally available natural products in some countries, mostly of herbal origin. New herbal preparations are being designed, tested and proposed for the local treatment of addicted people as cheap, affordable, alternatives to expensive Western medications. Both written and anecdotal reports indicate the extensive use of such medications in Asia (China, Thailand, Myanmar, Laos), designed to treat opium/heroin addicts. Similar herbal preparations are marketed in various European countries for the symptomatic treatment of alcohol- and nicotine-addicted people. The 'know-how' for such herbal remedies usually comes from local systems of traditional medicine, e.g. Traditional Chinese Medicine (TCM), the Indian Ayruvedic traditional medicine system, and European ethnomedicine. The recipes for such herbal formulae have been proposed/ developed by pharmaceutical companies, research establishments or by learned individuals. The main purposes of using such preparations include: inducing a rapid detoxification process; assisting/mitigating the withdrawal process; reducing both symptoms and signs of craving; helping the somatic body recover. Published, yet insufficient, evidence suggests that some of these remedies may have potential value and deserve further investigation and possible development into marketed products.

There are several reasons to explore the potential of using herbal and other CAM products for the treatment of various addictions:

- The tradition-based interventions, including the traditional herbal medicines, may be more socially acceptable in some countries than the approaches used in Western countries. In certain circumstances it may constitute the only acceptable approach for substance abuse treatment. The most familiar examples are opioid agonists, now widely accepted in the Western world as substitution drugs but totally unacceptable and unapproved for the same purpose in a number of countries.

- Use of herbal products may be cost-saving.

- Existing obstacles and difficulties in collecting, processing, validating and integrating traditional and modern herbal medicine.

- High prevalence of traditional medicine practice in a large number of regions of the world.

4.0 Country Profiles – the native use of herbal substances

The scope of national initiatives and studies ranged from focused research projects aimed at the verification of single plants/popular concoctions to the clinical testing of locally produced herbal mixtures in single- (i.e. Vietnam), or in multi-centre (i.e. China) trials. Several of these products are currently at various stages of clinical testing or are already locally used in treatment centres/clinics (i.e. China). A summary of individual country presentations is given below. Not all country profiles of those represented at the symposium are present in this section as some representatives chose to focus on a particular herbal substance rather than being country specific.

4.1 Brazil

In a search of a number of sources, including Brazilian books and dissertations in phytotherapeutics, PubMed, CAPES, NUPAUB-USP, and CEBRID, no published papers written by Brazilian authors were identified. There are only three short notes in the masterly book written by Shultes and Raffauf (i.e. The Healing Forest: Medicinal and Toxic Plants of the Northwest Amazonia. Portland, Oregon: Dioscorides Press, 1990). In Brazilian books on folk medicine, 8 mentions were identified; 6 of them dealing with treatment of alcohol problems and 2 with Ayahuasca. Local studies documenting the use of plants in rituals carried out by the Krahô Indians were carried out. The 2 years of fieldwork were guided by methods of anthropology and botany. The local shamans indicated 286 formulas, consisting of 138 plant species in 50 uses that could be associated with some type of action on the CNS. Out of these, 98 formulas, 87 plants and 25 uses appeared to involve psychoactive properties, such as: 'to get slow', 'stimulant effect', to 'calm down', to 'enhance memory', to 'reduce anxiety' and to 'induce sleep'. Phytochemical and pharmacological literature data were queried to establish any correlation between indigenous knowledge and scientific indications for each one of the 138 plant species. Studies were available for 11 of these plants; and for two of them scientific data coincided with indigenous information.

In Brazil, alcohol is the most serious substance abuse health problem. According to a 2004 survey on admission to 160 Brazilian hospitals, alcohol represented 75.7 % of the admissions, followed by cocaine (4.1%) and marijuana (1.3%). However, thousands of Indians and millions of "caboclos" were not represented in this survey.

Both the Brazilian Public Health System and Brazilian Medical Schools are well acquainted with international diagnostic criteria such as the ICD-10 and the DSM-IV. Pharmacotherapy of drug dependence in Brazil is based on drugs commonly used worldwide. About 70% of the Brazilian population is located near the coast; the very few people who live in the Amazon do not have access to medical resources from the public health system and have to rely on nature for their medicine. Consequently, the "caboclos" seek assistance from both "curandeiros" and "raizeiros". Indians are assisted by shamans or waiaca/healer men/ "feiticeiros". These "folk doctors" are not acquainted with academic medicine and therapeutics, and resort to local plants to treat different ailments. Furthermore, alcohol abuse and dependence are not recognised in accordance with the criteria of academic medicine. As a consequence the Indians, although involved in heavy alcohol drinking, usually declare alcohol as a "white man problem" and their shamans do not treat alcoholics.

4.2 Mexico

Herbal medicine, originating in pre-Hispanic times, is extensively used in Mexico where, following the Spanish conquest, herbal pharmacopoeia were enriched with substances imported from the old continent.
In Mexico, herbal medicine is not just a collection of recipes and ancestral procedures for healing

but also expresses the relationship between man and nature in a social context. It has been estimated that when the Spaniards arrived in Mexico in the 16th Century, the healing powers of approximately 2,000 plants were known. The importance of this type of medicine is linked to Mexico's privileged geographical location, which has some of the richest biodiversity in the world, coupled with a wide range of indigenous cultures.

In 1975, due to the influence of the World Health Organisation which recognized the value of traditional medicine in preserving the health of many societies, the Mexican Institute for the Study of Medicinal Plants (IMEPLAN) was created. For a period of five years, academics carried out a number of pieces of scientific research on traditional indigenous medicine. Compounds from different substances were isolated and medical properties tested, including: nopal (cactus leaf) (Opuntia sp) for the treatment of skin diseases, and as an anti-inflammatory remedy; tree daisy (Montanoa tomentosa) to facilitate the expulsion of the foetus and/or to aid the process of delivery; and white sapote (casimiroa edulis), as an anti diarrhoic agent. The widespread use of plants such as cudweed (Gnaphalium sp.), eucalyptus (Eucalyptus sp.), spearmint (Mentha sp.) and chamomile (Matricaria chamomilla) has also been documented. In the state of Hidalgo, an area with a large indigenous population, some 650 medicinal plants have been identified and 450 seem to possess therapeutic properties.

Herbal medicine is combined with medical treatment in certain rural localities. Some studies have reported that a high proportion of General Practitioners in urban areas also accept the therapeutic use of herbal medicine while a smaller yet significant proportion use it as a therapeutic resource.

Herbal medicine includes hallucinogenic plants, the most widely known being datura (Datura ceratocaula), peyote (Lophophora williamsii), morning glory (Turbina corymbosa) and hallucinogenic mushrooms or teonanacátl (Psilocybe and Stropharia). These plants were used in religious rituals and are still used by certain tribes. Peyote, for example, is used in the annual walk of the Huichol to meet the Gods. Huichol prepare themselves ahead of time and during the journey eat peyote, which reduces their need for water and meat. Traditional healers of certain indigenous cultures, such as the Mazatec, Mixe and Chinantec, use Psilocybe or Turbina corymbosa to help them in making a correct diagnosis or prescribing an effective treatment.

In 2002, a national household survey was carried out of the adult urban population of Mexico, representing 75% of the total population. This study, which was part of the World Health Initiative on Mental Health, included a section on traditional medicine. Although this survey did not include rural localities where the use of herbal medicine is more widespread, it shed some light on the acceptance of herbal medicine by the general population. The sample design, based on a strict probability selection scheme, was used to measure 17 DSM-IV psychiatric disorders and service use. A total of 5,826 completed interviews were obtained, with a response rate of 76.6%. It demonstrates that 23.7% of the population had a lifetime history of psychiatric disorders with a 12-month prevalence of 11.6%. The most common lifetime disorders were major depressive disorder (8.7%), specific phobias (7.3%), and alcohol abuse (4.4%). Of drug use, 10.4% of the population reported any illicit use in their lifetime; marijuana (7.8%) and cocaine (4.3%) were the substances most commonly consumed, with 2.3% of the sample reporting its use in the previous 12 months. Of the sample, 1.4% had a lifetime history of drug abuse/dependence, with a prevalence for the previous 12 months of 0.4%. Men were more likely to have drug abuse disorders, with a male:female ratio of 1.45:1 Eighteen percent of substance misusers reported having accessed some specialist services during the past 12 months, while 3% reported having joined self-help groups or used alternative medicine including herbal treatment. Three out of every 10 persons had used a herbal medicine, a practice that was more likely to be reported by females, by those in the age range 30 to 44 years, and by those with less education. Herbal medicine use was significantly higher among those with a DSM-IV psychiatric diagnosis (8.92%) compared with the population without a mental disorder (2.53%).

In order to complement this information, interviews were conducted among traditional healers who work in local markets and are known by the population for their treatment of substance abuse.

Substances used in the area of addiction included basil, for the treatment of gastrointestinal disorders; St. Ignatius herb (Ignatia amara or Hura polyandra), for the treatment of liver dysfunction; Hierba de toro (Bull shadow, Jodina rhombifolia) to deal with gastrointestinal disorders; zen leaf, to induce diarrhoea and thereby limiting the craving for the drug; and avocado leaf (Persea americana) used as an aphrodisiac.

4.3 China

The National Institute of Drug Dependence (NIDD), set up in 1984 by the Chinese Government, is the national centre of excellence for drug misuse research. Within NIDD, several herbal mixtures are at present in various stages of clinical testing in the form of multi-centre trials. Other herbs/herbal concoctions are already in use in Chinese treatment centres. Typically, herbal preparations are combinations of single herbs with widely accepted indications within the Traditional Chinese Medicine (TCM) framework. Any detoxification process, carried out using the TCM approach, is led by the principle that its use in treatment is to reinforce the healthy qi and eliminate the unhealthy qi; to resolve and expel toxins, and to focus on symptom-orientated intervention. Any research use, development, manufacture, and distribution of newly developed detoxification drugs must be approved by the appropriate regulatory authorities.

The testing protocols are designed to comply with international standards, including the use of reference compounds (clonidine and lofexidine), and the evaluations completed so far are reported to give some ground for optimism. A few other preparations have already been approved by the national health authority for large-scale use. The history of opium abuse in China dates back to the 19th century and many herbal compounds have been applied to the treatment of this problem since that time.

The 'general effect' theory involves both a primary (Bin) and a secondary pathogenesis (Biao). Four regular components have been identified in Chinese herbal medicine products:

- Principles: components responsible for the therapeutic effects
- Adjuvants: assist 'associates' in decreasing the compound toxicity/side effects
- Messengers: help the drugs to arrive at their targets

Since 1993, a number of trials have been completed.

Table 1.

Chinese herbal preparations used in clinical trials in China

Product name	Status	Intended use / indication(s)
Fukang tablets	Clinical trials completed	opioid detoxification
Lingyi tablets	„	opioid detoxification
Anjunlin tablets	„	opioid detoxification
Shenfu capsules	„	opioid detoxification
Taikangning capsules	„	opioid detoxification
Fuyuan granules	„	opioid detoxification

A few randomised, controlled, double blind, multi centre trials versus either clonidine or lofexidine have been carried out with different herbs between 1992 and 2005 in West China hospitals.

Efficacy findings: 50% to 80% of clients reported beneficial effects with the use of these compounds. Furthermore;

- Adverse effects of Fukang were found similar to those of Clonidine.
- LingYi was better tolerated than clonidine and equal to placebo.
- Shenfu tablets side effects placed between placebo and clonidine.
- Most frequent side effects of Taikangning: blurred vision (40%); dry mouth; nausea.
- Typical dosage of the herbs was 5-6 grams three times a day.

Taikangning contains:

- Principal compound: Ginseng
- Associate compounds: Yanhusuo (which arise from Corydalis), and Dandelion (which arise from Taraxacum)
- Adjuvant: Datura flower

Datura seems to be the most powerful compound included in the mixture. However, 'principal' compound, in this context, does not necessarily mean the active, most powerful, compound. Principal (Ginseng) is a stimulant (YANG) and is meant to be there to reverse the sedative (YING) issues caused in the long term by opiates

It may be concluded that:

- Withdrawal symptoms may improve with the use of these herbal compounds.
- Side effects are moderate.
- A typical treatment is 10 days long.
- Herbs should be administered together with methadone in the first few days of treatment.
- Maintenance with herbs may be considered to cope with the secondary withdrawal syndrome.

4.4 Ghana

In Ghana traditional medicine is an ancient phenomenon and one could argue that its 'survival proves its efficacy'. Drug abuse is a relatively new phenomenon and the use of herbal medicine in the treatment of addiction is very recent.

Seventy percent of the rural population of Ghana access traditional medicine because of a number of factors, which include:

- Easy access
- Minimal bureaucracy
- Affordability of treatment
- Paucity of side-effects
- Closeness to people beliefs
- Failure of orthodox medicine in chronic cases.

Elements of traditional medicine in Ghana include the following:

- Herbs
- Psychic and divine healing
- Faith-based healing
- Traditional birth attendants
- Bones setters and circumcisers
- Mixed type

Many traditional medicine professionals claim to treat all conditions. There are about 20,000 traditional medicine practitioners in Ghana, far more than orthodox practitioners:

- Traditional healers: general population= 1:100
- Orthodox doctors: population= 1:10,000

In Ghana, the healers' education is officially promoted and research on herbal medicine is actively encouraged. At the moment, traditional medicine is being modernised, with better technology in

packaging the products. There is now a University Centre for Research and Scientific Studies (CRSS) into plant medicine and a degree in herbal medicine is currently delivered by one of the Ghanaian Universities. The CRSS is more than 30 years old and has researched and catalogued some 450 medicinal plants and herbs.

A number of anecdotal reports of success in the treatment of alcohol dependence with the use of herbal medicine were reported by the Ghanaian delegate. Most mixtures involved mango flowers and ginger and these herbs allegedly need to be administered only once.

4.5 Vietnam

The official number of drug addicts in Vietnam has been estimated at 180,000 since the mid-nineties. Today, the figure may be considerably higher than that. Some addicts are South Vietnamese war veterans who picked up the habit after being given morphine in hospital. A dramatic increase of drug abuse is recorded in urban agglomerations. This group appears to correspond to Western recreational users, abusing an increasing variety of drugs including heroin, cannabis and synthetic drugs. Finally, there is a high concentration of opium abusers among the hill tribe members, especially in the north, where opium is traditionally produced and consumed as a social drug. Government treatment and rehabilitation efforts focus on opiate addiction. A complex pattern of private, humanitarian, social, religious and government operated addiction treatment facilities for opiate addicts operate in Vietnam. The roots, origins, and also the treatment methods vary from tradition-based village healers using herbal concoctions of unknown composition, efficacy and safety to substitution with opium/opium tincture, or methadone.

Herbal treatment has a long tradition and a wide acceptance in the Vietnamese society. Its roots, philosophy, and many of the herbal ingredients used tend to overlap with those in South China (see below). The great majority of herbal medicine users in Vietnam live in rural areas, and are often self medicating with herbs in the absence of more advanced medical and pharmaceutical services. The Ministry of Health conducts an active campaign to revitalise and revive traditional medicine, including the 'Drugs at Home' and 'Doctor at home,' as well as the national policy for traditional medicine through 2010 encouraging communal clinics as well as villagers to grow essential medicinal plants known for their healing properties. Regulating the practice of traditional herbal medicine has been an integral part of the Vietnamese government's programme to promote traditional medicine since 1955. As a result of this, Vietnam is one of the few countries in the world that is seen to have an integrated approach to health care, with traditional medicine playing a substantial role in medical education, research and practice (Walhberg, 2006). Traditional medicine practitioners can be classed into three different groups: elder practitioners who have been trained in classical traditional medical techniques with a classical theoretical and philosophical base; those who have received training in traditional medicine faculties of medical colleges and finally the 'herb doctors' who have received no formal training but acquired knowledge and experience through apprenticeships. In Vietnam today, it is by far the latter two groups who provide the majority of medical treatment. The regulation of the practice of traditional herbal medicine has happened through two specific routes: first, by making both modern and traditional medicine compulsory components of medical education and practice in Vietnam; and second, by the organisation of apprentice-trained 'herbal doctors' into national associations as well as the development of a licensing system for these practitioners.

Heantos

In the early 1980s a herbal scientist from Ha Tay province, west of Hanoi, proposed a concoction of bark, stems and leaves of some 14 or more herbs for the treatment of opiate addicts. The product was given the fantasy name Heantos. The exact composition (correct botanical specification and the relative proportions of the ingredients) of the mixture has not been disclosed. According to the inventor, Heantos is a traditional oriental medicine, the recipe was derived from the hill tribe usage of local herbs to keep the opium withdrawal symptoms at bay. The plant mixture is extracted with boiling water and then concentrated. The product originally used was a foul-tasting syrup; subsequently, it was produced in capsule form.

After an initial phase of sporadic applications, evaluation of Heantos, with government approval, started on opiate addicts in 1990. It is claimed that by 1996 more than 3000 people had been treated with Heantos as a heroin / opium detoxification agent with an overall relapse rate as low as 20% after the first phase of treatment. The drug was used as part of a complex treatment that included acupuncture, massage, and inhalation of aromatic oils. The duration of in-patient treatment was 7-10 days. The concoction was claimed to be very cost effective, with figures in Vietnam ranging from 70 to 300 US dollars per patient.

From the late 1990s, toxicity studies and clinical trials have been agreed and started in the USA (Johns Hopkins University, NIDA), in Germany (since 2001 in Essen) and Denmark and funded from various bilateral and multilateral sources (e.g. UNDP and UNOPS, UNESCO; while WHO and the UN drug control bodies did not join). Studies that have taken place at the Vietnamese Institute of Chemistry in Hanoi, have shown that 107 patients who became addicted to the pain-killer morphine in the course of their treatment, were given Heantos, and 72 stopped requesting their morphine doses. Furthermore the Institute claims that the tablet form of the medicine prevents former addicts from returning to drug use. This medicine, Heantos-1, is said to have a deliberately negative side effect: should a patient slip back into drug use, he will suffer painful, convulsive fits.

The Government of Vietnam gave its consent and initial support to the use of Heantos and also to the international cooperation, but appears to have lost interest subsequently. Nevertheless, according to available information clinical trials were still ongoing in Germany and Denmark as late as 2002. According to some (non-confirmed) sources, the formula of Heantos has been split into two and a new Heantos-2 was being used in later years. Unfortunately, no formal reports or published validated results seem to have been published as yet on the outcome of the above efforts. Hence, evidence of the medicine's effectiveness is largely anecdotal. No follow-up studies on whether patients remain drug free have been undertaken, nor have there been scientific studies of possible side effects.

Various Vietnamese sources indicate that a separate effort started in 1992 using another traditional herbal formula derived from doctors in the ancient Vietnamese high society. This formula consists of 16 plants. Composition, dosage and treatment regimen were disclosed, (but neither the proportions of the herbal constituents, nor the processing method). The product is named Vinantidic-TKC. Latest reports on the development, initial toxicity studies, first clinical trials in Vietnam, date back to 1992/1993. The product appears to have been approved by the Vietnamese Ministry of Interior and the Department of Public Health (Report of Min. of Interior with General Department and Department of Public Health, Socialist Rep. of Viet Nam, Hanoi, June 1992)

Given that Heantos is such a complex mixture, satisfying the demands of regulatory authorities has been a persistent problem, even a 2004 European Union (EU) directive, designed to lower the hurdles for certain herbal remedies, doesn't provide much assistance (Nature 433, 2005). Non-disclosure of the constituents of the composition will remain an obstacle for the evaluation of the safety, efficacy and usefulness of any composite herbal medicine. In many countries the detailed composition of products including food and beverages is required by law and for medicine of course there is no exception.

The expert group believe that individuals with addiction problems are very vulnerable and their rights to safety and protection has to be respected and adhered to at all times.

Although a senior scientist member of the expert group from Vietnam was present at the meeting, no further information on Heantos was made available.

CMT

CMT (the product is currently known only by this acronym) pills contain 5g of active ingredients and includes a concoction of 27 herbs (data on its composition are available, upon request). Before being allowed to be administered in clinics, the CMT compound went through a number of acute and subacute toxicological tests and was reportedly found to be both safe and non-addictive. Tests were carried out at the Institute of Drug Quality Control, Department of Experimental Traditional Medicine; Vietnam Traditional Medicine Institution.

It was stated that to get the product patented, the Vietnamese centre will have to complete the enrolment of some 360 clients; only 40 have been recruited so far during an 'open label' study in which above number of opiate addicts were tested 1, 3, and 5 days after CMT administration. To be included in the CMT study, patients had to be diagnosed as suffering from either heroin and/or opium addiction. Those suffering from a number of conditions, including: heart; liver; kidney failure, asthma, dermatological diseases; hypertension, cancer or who were pregnant were excluded.

Overall, thirty-five patients showed excellent, and 5 of them good, results. According to this study, it took about 20 minutes for CMT to produce a withdrawal reduction level, but most significant clinical results were observed on days 4 and 5 of CMT treatment. Apart from one report of dizziness and headache during the CMT trial, no further adverse events were identified. Thirty-six patients out of 40 were surveyed 2-6 months after having been discharged from the hospital. Method of surveillance included: a) interview of the index patient's family members; b) urine tests for opiates. Apparently, however the vast majority of clients previously detoxified through the CMT procedure were found to have relapsed into drug use. The relationship between CMT and previously used/well-publicized, Vietnamese, herbal mixtures is unclear.

4.6 Hungary

There are a number of over the counter (OTC) herbal preparations licensed as of 1986 in Hungary which possess some specific indications for the treatment of alcohol and tobacco addiction (Table 2).

Table 2

Herbal products licensed for addiction treatment in Hungary

Preparation	No. of herbal constituents	Purpose/suggested mechanism
Alcohol		
Dezalko anticraving tea	8	craving reduction
Dezalko anti-anxiety tea	8	anxiety reduction
Dezalko detox- and hepato-protective tea	9	hepatoprotective
Tobacco smoking		
Antismoking herbal tea	3	abstinence maintenance
Nicobrevine capsules	5	abstinence maintenance
Nicogelat capsules	5	abstinence maintenance
Nicorazil capsules	6	smoking reduction
'No smoking' tablets.	5	smoking reduction

Common characteristics of the tea mixtures licensed in Hungary include the following:

1. They are multicomponent mixtures by using herbs with traditional reputation of being 'useful' as home remedies for alcoholics or nicotine addicts. No plant with known specific receptor effect is used in these preparations; their use is based either on a proven effect on anxiety and depression, or on the body´s metabolic processes.
2. These preparations were 'developed' by herbal scientists only some 20 years ago, based on a

blend of locally available know-how/traditional experience and of the experience derived from knowledge of modern phytotherapy. Hence, they cannot be considered as completely traditional herbal products.

3. Certain ingredients of these herbal teas (e.g. Hypericum, Valerian, Melissa, Silybum) also serve as raw materials of pharmaceuticals registered/licensed in Europe and elsewhere for nervous or metabolic disorders. Their use is spreading and sales' values are growing faster than the average growth rates of pharmaceuticals in general.

5.0 From traditional use to basic research and clinical practice

Efforts to explore the scientific and practical potential of already known pure natural compounds, alkaloids (e.g. lobeline, ibogaine and other indole alkaloids), and non-nitrogenous compounds (cannabinoids, certain flavonoids) for addiction treatment have intensified in recent years. This may be seen as a late recognition of two important facts:

- Many pharmaceuticals used today in the treatment of addictions have had their origin and root in nature;

- Contrary to many other areas of therapy, the reservoir offered by nature has not yet been fully explored. However, several popular medicines of vegetal origin do have a local reputation and are being used by and for drug addicts. Similarly, an array of plants has been used locally to alleviate alcohol or tobacco craving or as adjuvants in the pharmacotherapeutic plans. However, very little effort has been devoted to the verification of such claims. Hence, the practice of using herbal products in drug addiction treatment remains mostly local and the information available continues to be rated as both anecdotal and of questionable reliability.

5.1 Kava

Research into Kava (Piper methysticum), a popular beverage in the South Pacific islands where it is not considered an addictive substance, has identified seven pyrones as major components, including kavain and others.

Kava may be classified as a minor tranquilliser and its pharmacological effects include:

- Sedation
- Potentiation of other sedatives
- Anticonvulsant activities

It has been suggested that Kavain inhibits the veratrine-induced increase in intracellular calcium and glutamate release, possibly by inhibition of voltage-dependent sodium channels.

Kava was withdrawn from the market a while ago because of liver failure reports after human use. In regards to hepatotoxicity, 78 cases have been already reported, of which 11 required liver transplants. Four resulted in hepatoxic deaths which were probably linked to cytochrome P450 inhibition and/or to a reduction in liver glutathione content and/or to the inhibition of cyclooxigenase enzyme activity (Cote et al 2004). However, several clinical trials have confirmed both anti-anxiety and anticonvulsant activities of Kava.

It is believed that kava spissum, but not kavain, may inhibit the long term potentiation (LTP). Different from benzodiazepines, kavain does not inhibit the LTP mechanisms. As a result, this suggests that kavain does not cause those cognitive effects so frequently seen with benzodiazepines. Whereas in aqueous extracts the glutathione is extracted along with the

benzodiazepines. Whereas in aqueous extracts the glutathione is extracted along with the kavalactones, in acetone or alcohol solutions glutathione is not extracted. This might possibly explain why the indigenous Polynesian population using a water based solution have not developed significant liver problems, whilst medicinal use mostly relying on acetone or alcoholic extracts has led to reports of liver toxicity (Cote et al 2004). However, until this hypothesis is confirmed, patients should be advised not to take Kava.

5.2 Wilthania somnifera (ASW)

Research related to Aswal (Withania somnifera), an indigenous plant of India, shows wide usage in Ayurvedic and Sidda medicine as a sedative. Some preliminary suggestions for its use in anxiety and depression have already been published, but no Randomised Control Trials (RCTs) have been carried out so far. Its anticonvulsant effects have been confirmed in the low magnesium models of epilepsy. Aswal leads to LTP decrease, which suggests that it may be used to treat anxiety during opiate withdrawal (Kulkarni and George, 1996).

Ayurveda is based on the Hindu scriptures. In Ayurvedic medicine, herbs are only one of the elements of the holistic treatment. Herbal medicine compounds are not required to go through phases 1-3 before being introduced into the market in India. In particular, no animal toxicology or clinical trials are required for the marketing of specific products in that country. Ayurvedic practitioners undergo a specific training; they use a traditional system of diagnosis and classification of illness. Herbal research in India is restricted to animal studies; no clinical studies (or only a few, but of very poor scientific quality) are available. No funding is provided to researchers.

The active component Wilthania somninifera (ASW) is mainly obtained from the plant root and contains several components whose action is mainly related to interaction with both GABA and 5-HT systems. It is claimed to possess a number of properties, including: neuroplastic; pro-cognitive; antidepressant; anxiolytic; antioxidant; anticancer; immunogenic; and hepatoprotective (Kaur, 2004). Furthermore, an attenuation of both opiate dependence and withdrawal symptoms have been observed with the use of ASW (Kulkarni and Ninan, 1997). ASW seems to accelerate the alcohol detoxification process after a binge.

Pharmacodynamics: the interferes with the binding of GABA to GABA sites and increases chloride influx in the absence of GABA (Mehta, 1991). From this point of view, it should be considered an anticonvulsant compound. Furthermore, ASW down-regulates the 5HT1 and up-regulates the 5HT2 receptors (Tripathi, 1998); inhibits both AchE and BuchE; increases the number of M1 amd M2 receptors; and inhibits calcium influx into the cells without inducing hypotension (Choudhary et al 2005).

Withanolide A, one of the components of ASW seems to possess neuroplastic effects, being able to reverse the amyloid–beta induced loss of axons, dendrites and synapses found in dementia. Benefits are reported to be dose- and time-dependent. Pro-cognitive effects with ASW are reported as well, since it may improve retention of passive avoidance learning.

Anti-stress/anxiolytic/antidepressant activities: in animal studies, it appeared that ASW was equal to lorazepam in models of anxiety. Furthermore, ASW was equal to imipramine in models of depression. ASW inhibits stress-related reactions in animal models of stress, such the foot/shock ones (Bhattacharya, 2001). Fifty patients with anxiety disorders were administered with an ethanolic extract of ASW, at the dosage of 250 mg BD. Moderate to excellent improvement was obtained in 72% of patients. In a further randomised controlled trial vs. placebo, 39 clients were allocated either to 1.0-2.5 grams of ASW daily or placebo; an equal number of dropouts was observed in both groups. The response rate at 2 weeks was 71% for ASW and 38% for placebo. At 6 weeks, the response rate was 88% for ASW and 50% for placebo. No discontinuation nor rebound effects were noted upon the abrupt discontinuation of ASW at 6 weeks. However, it is not clear if this was due to the very long half-life of ASW metabolites.
ASW is used Ayurvedic medicine to protect both the liver and the kidney. ASW intake may deter-

ASW is used Ayurvedic medicine to protect both the liver and the kidney. ASW intake may determine some increase in immunocompetence, having showed antibacterial activities against a range of micro-organisms (Agarwal et al, 1999).

Adverse effects:

- Coagulation time may be increased during ASW treatment; returning to normal after one week of treatment withdrawal.
- (High doses): increase in cathecolamines.
- T4 and possibly T3 levels increase. Thyrotoxicosis reported in a healthy woman taking ASW; this disappeared when ASW was discontinued.
- (High doses): libido reduction and decrease of sexual performances
- Increase in body weight.

Drug interactions are suggested to be unlikely because ASW does not interact with CYP450 enzymes. Doses of up to 4.0 grams over dose may be fairly well tolerated.

5.3 Ayahuasca

Ayahuasca contains harmala alkaloids from the bark of a vine, Banisteriopsis caapi, and typically has DMT from the leaves of the shrub Psychotria viridis. These two plants grow in the hot river regions of Northern Brazil and neighbouring countries. Ayahuasca has a long history of traditional and ceremonial use in medico-religious practices throughout the region. The main harmala alkaloids in Ayahuasca include: tetrahydroharmine (THH), harmaline and harmine. B. Caapi vine samples may contain different concentrations of THH, harmine and harmaline. P. viridis is a member of the Rubiaceae plant family, which also includes the coffee plant. DMT is actually produced in the healthy mammalian brain and is rapidly metabolized by the enzyme MAO-A.

DMT is fully psychoactive when injected, inhaled or insufflated. It is orally active only when MAO-A is inhibited. The DMT psychoactive effects last for 5–30 minutes when MAO-A is not inhibited; visual hallucinations are reported in 100% of human volunteers when DMT is injected in sufficient amounts. Ayahuasca use has been reported to cause collective perceptual alterations, i.e. 'shared' visions, which certainly reinforces its traditional and contemporary usage as a religious sacrament.

Most of the recent scientific information on Ayahuasca became available from the 'Hoasca project', which started in 1993 with the help of the UDV ('Uniao do Vegetal'), a religious group in Brazil. It appears that the time of collection of the P. viridis samples is critical, with the highest DMT content being found in samples collected in the early morning or late afternoon. The preparation of Ayahuasca takes many hours; and different Ayahuasca preparations may contain different concentrations of the active alkaloids. Nearly half of the 15 UDV volunteers who gave a blood sample after having taken Hoasca (Ayahuasca) appeared to be slow metabolisers of harmine. Although both DMT and THH metabolisms were similar in the 2 groups of individuals (i.e. slow vs fast metabolisers), long term changes (e.g. 30 days since their last exposure to Hoasca) were observed in terms of upregulated peripheral 5-HT reuptake sites, in blood platelets (Callaway et al, 1994). In particular, the Bmax of the platelet 5-HT reuptake site was significantly increased in the Hoasca drinkers when compared to age-matched controls. Since these individuals drink Hoasca on a weekly basis, it is believed that CNS synaptic plasticity is altered in a way that more receptors are likely to be produced to cope with the 5-HT increase caused by the Hoasca intake itself. A preliminary SPECT study showed that a similar long term change occurs in human brain 5-HT reuptake sites after exposure to these harmala alkaloids.

Grob et al (1996) assessed the psychological status of 15 long term members of the UDV and found evidence of their high functional status, despite a history of substance misuse in most of these men before they joined the UDV. If Hoasca is taken with serotonergic drugs, such as the SSRIs, the 5-HT syndrome may occur (Callaway and Grob 1998). Hoasca psychoactive effects might be considered to be associated with a significant acute increase in serotonergic activity,

which subsequently leads to increased turnover and receptor up-regulation at both central and peripheral levels. Tolerance to this serotonergic effect does develop, as evidenced by the increase in platelet 5-HT reuptake sites (Callaway et al.,1994), which may be behind the appearance of the purported therapeutic effects.

In both traditional and contemporary usage, Ayahuasca is not primarily used as a treatment for drug addictions. However, it is already used in the clinical practice of at least one medical doctor in Peru and may have a promising future in the herbal treatment of addictive disorders.

5.4 Kudzu (Pueraria lobata)

Originating from China and Japan, it may have been used over the last 400 hundred years as a medicinal plant. It may help in overcoming the hangover effect of recent alcohol intoxication (Shebek and Rindone, 2000). Given to rats, it may decrease voluntary alcohol intake by 30%; no tolerance to effects of Kudzu seem to be reported. Another study involved alcohol, where alcohol-preferring hamsters were given Daidzin, disulfiram or placebo. Treatment in the Daidzin group was associated with an 80% reduction of alcohol intake.

Lukas (2005) administered eleven non-dependent heavy drinkers with either 19% puerarin, 4% daidzin or 2% daidzin. Seventy-three percent of those administered with kudzu drank significantly less, possibly suggesting a binge-drinking limiting activity. Another study involved thirty-eight alcohol dependent patients administered with either kudzu or placebo. Although the mechanism of action was unclear, encouraging results were reported.

5.5 Hypericum perforatum (St John's Wort) and alcohol addiction

Mechanisms of alcohol dependence are basically unknown and thought to be non-specific. Conditioned learning and reinforcement issues should be considered as essential elements in the establishment of alcohol addiction. Both the DA and the glutamate system are important for the understanding of alcohol pharmacodynamics. Mechanisms involved in the development of maintenance of addiction include both positive reinforcement, which occurs through DAergic and opioidergic mechanisms, and negative reinforcement which is both linked to stress and withdrawal and motivating the individual to drink alcohol.

Early herbal treatment of alcoholism included the use of Atropa belladonna and of Strychnine. Hypericum perforatum contains mostly hypericin and hyperforin. It is possible that Hypericum may act on central 5-HT mechanisms, commonly altered in both alcohol and depression. Animal studies: a dose-dependent reduction in alcohol intake was observed by Rezvani (1999). Perfumi (2005) administered Hypericum to a sample of Sardinian alcohol-preferring rats and results were encouraging. Another study involved the administration of Hypericum to alcohol-deprived rats and a further study compared (in animals) imipramine, fluoxetine and Hypericum extracts. It was suggested that Hypericum may act synergistically with naltrexone in the treatment of alcohol dependence.

Hypericum increases the LTP; furthermore, it might act as a non-selective re-uptake inhibitor of GABA, serotonin and others (Nathan, 2001). Its stimulant effects seem to be mediated by both activation of the AMPA receptors and by inhibition of GABA-A/GABA-B receptors.

The usefulness of hypericum in addictions may lie in the treatment of concomitant depression. However, treatment with hypericum during alcohol withdrawal can lower the threshold for seizures (Darton, 2002)

5.6 Ibogaine

This substance, reported to be initially misused in the 1960s, was made illegal in the 1970s in the US. It seems that during the 1980s some research on this compound was funded. 'Underground' research on ibogaine began in the 1960s for the treatment of heroin addiction, which continues to this day in several countries. It is primarily used for alcohol, heroin and cocaine addictions.
Rezvani (1995) found that intraperitoneal, but not subcutaneous, ibogaine intake reduced alcohol self-administration in animals. In a subsequent study, Rezvani (1997) found a dose-dependent decrease in alcohol intake and preference in laboratory animals. Effects on 5-HT, DA, NMDA and opiod receptors were reported. The nor-ibogaine metabolite has a longer half-life than the parental compound, but is not as effective in treating addictions.

Cerebellar degeneration has been reported in rats administered with ibogaine. It is felt that absence of similar findings in mouse experiments cannot imply that ibogaine is safe in humans. Between 1990 and 2006, 9 deaths after ibogaine use were reported. More deaths may have occurred but not reported due to the "underground nature of ibogaine treatment". One death occurred at 4.5mg/kg per os, a much lower dose than used in the rat experiments.

5.7 Sceletium

Data from both literature searches and reliable convergent folk anecdotal use would suggest that preparations of the plant Sceletium may have effective hypnotic, minor tranquillizer and anti-spasmotic activities (Herre, 1971). Additionally, it may be useful in the treatment of drug-related issues. Two key informants, both renowned traditional healers, reported that a fermented Sceletium product, kougoed, can be used to assist in weaning alcoholics off alcohol, and that they had experience in successfully treating alcoholics with the anti-craving product kougoed. A disulfiram-like effect can also be achieved by adding some freshly squeezed Sceletium juice into a bottle of wine or other alcoholic beverages. The drinker will feel extremely nauseous and sustained aversion to alcohol will result.

Apparently, enough plant material has been gathered from the wild in an ecologically acceptable manner for basic chemistry, receptor-specific assays, and limited phase 1 trials being possibly carried out. Plant material is currently being propagated from seed, from cuttings and from tissue culture to investigate the potential for mass-propagation, as there is insufficient wild material for large-scale ecologically sustainable harvesting.

Sceletium properties depend on the method of preparation, season of collection, route of administration and dosage. Side effects may include light-headedness, drunkenness, nausea, headache, anorexia, and depression. Sceletium preparations are reported not to be addictive. If administered for specific indications, in lower doses, and for a limited period of time, kougoed may be seen as a medicinal preparation and not as an intoxicant. Small scale pilot trials are currently designed for the treatment of nicotine, alcohol and other problematic drug-related issues in South Africa (Gericke, 1995)

6.0 Overview of related international clinical research and status of use of herbal substances in the treatment of addiction

The International Expert Group in its examination noted that not much innovative Research and Development (R&D) work on plants specifically directed towards drug dependence has been either funded or carried out so far. Nevertheless, a few products (i.e. isolates from plants; synthetic copies and/or analogues), are in various stages of development, inter alia, for the purposes of addiction treatment.

Some of the best known examples are given in Table 3.

Table 3

Compounds of herbal origin in various stages of Research and Development work

Compound	Derivatives	Status	Expected use
lobeline	+	?	tobacco smoking, stimulants
cytisine	+	?	tobacco smoking
epibatidine/derivatives	+	clinical	tobacco smoking
THC/rimonabant	antagonist	clinical/approval	multiple
Ibogaine derivatives	+	clinical	multiple
ayahuasca alkaloids		clinical	multiple
kava-pyrones (withdrawn from the market)		approved	anxiety

A few examples of the different plant species used by indigenous populations on various continents as substitutes or specific antidotes for local psychoactive plants are summarised in Table 4. It cannot be predicted which avenue should be followed for each individual herbal medicine product. However, the new European 'Traditional Herbal Medicine' regulation appears to be a pragmatic, though not an easy, avenue for such products.

Table 4

Plants used locally as substitutes/remedies

Plant	Part / Form	Country	Status
Substitutes/Antidotes for opium			
Papaver somniferum	poppy capsule (tea)	India	authorised use
Mitragyna speciosa	kratom (leaves, extract)	Thailand	traditional
Lactuca virosa	lettuce opium (extract)	Turkey	traditional
Duboisia hopwoodii	pituri (extract)	Australia	traditional
Substitutes / Antidotes for tobacco smoking			
Lobelia sp.	tupa (smoked / tea)	Latin America and other regions	previously official neglected today
Cytisus sp.	herb (tea)	Europe	traditional
Datura sp.	leaves (smoked)	Europe/N. America	previously official; neglected today
Peganum harmala	leaves (tea)	Europe, Americas	traditional
Piper methysticum (Kava)		Oceania	smoking cessation
Thevetia thevetioides (Yoyotl)		Mexico	Unkown
Substitutes/antidotes for alcohol			
Withania somnifera (Ashwagandha)		India	craving for alcohol
Pueraria lobata (kudzu)		China	reduces drinking
Banisteriopsis caapi (ayahuasca)		Latin Am.	ceremonial use
Hypericum perforatum		Europe, etc.	reduces alcohol consumption.
Mangifera ind. + Zingiber off. (Mango flowers + Ginger)		Ghana	traditional
Opuntia ficus indica		tropics	hangover
Borago officinalis (oil)		Europe	hangover

Substitutes/antidotes with mixed use		
Mitragyna speciosa (Kratom)	Thailand	nicotine/stimulant substitute
Psychotria viridis (leaves)	Latin-Am.	part of ayahuasca preparation
Thunbergia laurifolia (?)	?	psychostimulant substitution
Astragalus membranaceus (roots)	China	opium addiction
Eugenia aromatica (?)	China	„
Panax ginseng (roots)	China	„
Ziziphus spinosa (seeds)	China	„
Corydalis ? (rhizom)	China	„
Datura alba (flowers)	China	„
Chelidonium majus (herb)	China	„
Aconitum lateralis (roots)	China	„
Angelica sinensis (roots)	China	„
Pinella asiatioca (rhizom)	China	„
Polygala ? (roots)	China	„
Lonicera japonica (flowers)	China	„
Gossampinus malabarica (?)	China	„
Cucurbita pepo (?)	China	„
Glycyrrhiza glabra (roots)	China	„
Silybum marianum (herb + roots)	China	„
Hedyotis diffusa (?)	China	„
Snake venom	China	„
Plants with general tonic and/or metabolic effects used as adjuvants		
Panax ginseng, Ginkgo biloba, Oenothera biennis (evening primrose), Silybum marianum, Taraxacum officinale, Echinacea purpurea, Withania somnifera, Banisteriopsis caapi		

A considerable amount of clinical research work with specific therapeutic purposes is in progress in a number of countries. (Table 5)

Table 5

Plants in various stages of pharmacological and /or clinical research

Plant	Anticipated use
Hypericum perforatum (Europe)	symptomatic treatment, cocaine addiction
Ginkgo biloba (China)	symptomatic treatment, cocaine addiction
Withania somnifera (Ashwagandha) India	symptomatic treatment opiate/ alcohol addiction
Lobelia sp.(North America)	as a source of lobeline, nicotine addiction
Tabernanthe iboga (West-Africa, Canada)	as a source of ibogaine, multiple uses
Pueraria lobata (Kudzu) (China)	alcohol addiction
Sceletium (South Africa)	symptomatic treatment, alcohol and drugs
Banisteriopsis caapi (Latin America)	addiction interruption and maintaining abstinence

7.0 Herbal medicine for the treatment of substance misuse; opportunities and limitations

There may be 5-15,000 herbal products in the UK market, but the current situation will change in the next 7-8 years when, according to EU directives, only licensed products will be made available to the general public. Herbal medicine products are now clearly and formally defined by EU regulatory agencies. Two main groups have been identified: herbal medicine products that are well established and herbal medicine products that can claim long-term traditional use. The EU traditional

traditional herbal medicine products directive was implemented in October 2005, but there will be a 7-year transitional period before this will be in full force. During this period, all EU member states will need to set up a new national scheme for the registration of traditional herbal medicine products. Both quality and safety will need to be demonstrated for most herbal medicine products. For traditional products, there will not be any requirement to demonstrate efficacy but instead a length of traditional use for 30 years, including at least 15 years within the EU, will need to be established.

It is suggested that any herbal preparation used for the treatment of drug addiction should meet the following criteria:

- Possession of a full marketing authorisation
- Completion of a full assessment of potential risks of addiction

In the EU pharmacopoeia, some 150 monographs on herbal drugs have been published so far. Traditional herbal medicine products are to be considered as medicines. However, according to some US studies, some 75% of herbal products include toxic and/or contaminated plant material and are of poor quality preparations.

The possibility of potential side effects and drug interactions from the use of herbal compounds is largely unknown. As a first step, one could conclude that already licensed herbal medical products should be assessed for efficacy and safety in pilot clinical trials.

8.0 From tradition to standardised products

With regard to the place of herbal remedies in addiction treatment, the following strategy should be considered:

Stage I: Information

a. A global call for information on herbs and herbal products used locally and/or thought to possess CNS effects that may be potentially useful in addiction treatment; inventory and basic evaluation of information.
b. Criteria and guidelines for ranking the most promising herbs and products for further study.
c. Critical assessment of available information on botany, chemistry, experimental pharmacology, toxicity, available for each 'high priority' natural product.

Stage II: Product acquisition, characterisation

a. Disclosure agreement with the product and/or know-how owners on:
    - Herbal constituents, proportions
    - Raw material collection – locations, period of the year
    - Availability of index plants in the indigenous flora; environmental consideration
    - Extraction process, strength, application/use, dosage, storage, etc.

b. Phytochemical research to be carried out, aiming at separating, isolating and characterising the active compound(s).
c. Analytical methods suitable for product characterisation and standardisation (if active principles are found and identified).
d. Chemical stability testing on the herbal product, using the active principle.
e. Comparative extraction and drug formulation studies: aqueous tea, tincture, solid extract, capsules, tablets, etc. as most suitable for local treatment environment.
f. Production of a standardised extract/concentrate whilst retaining its original composition and quality. This standardised product must be suitable for further research to be carried out.
g. Computer-assisted molecular modelling of active ingredients.

Stage III (part A): Preclinical pharmacology

a. Hypotheses concerning the mechanism of action of the herbal mixture, based on information derived from local use, to be formulated.
b. Confirmation using of both in vitro and in vivo studies.
c. Qualitative and quantitative description of the effect(s).
d. Acute, sub-chronic and chronic toxicity evaluation.

Stage III (part B): Clinical pharmacology (to be carried out only if safety data are satisfactory)

a. Human clinical trials to be carried out within target population.
b. Determination of product efficacy and safety; comparative studies to be carried out vs reference drugs.
c. Dose-finding studies.

R&D and Production Strategy

To ensure credibility, the following suggestions might be taken into account:

a. To consider only proposals with sufficient credibility, actual local use and some scientific probability of success.
b. To accept for consideration and/or testing only local herbal products with known or accessible composition.
c. To give the highest priority to products which offer promise for the treatment of addictions for which no effective treatment is now available.
d. Ensure sufficient availability of reliable raw material, as well as government endorsement and support to guarantee smooth, uninterrupted work.
e. Secure local and international participation and funding.
f. Negotiate and agree on ownership and use of the results and products, unless this information is already in the public domain.

9.0 Conclusions and recommendations

During the 1990s, the WHO encouraged the integration of herbal medicine into the national health care systems of countries, providing options for cheaper medication in developing countries. However, the focus to date has mostly been on the use of herbal medicines in general (e.g. for the treatment of malaria), and not for mental health specifically and particularly not for drug addiction. There are a number of inequalities related to the provision of treatment for drug addiction. In some countries, there are large number of patients suffering from alcohol and other drug problems but there is very little accessibility to effective pharmaceuticals. In several regions of the world, and for a number of economic, socio-cultural and religious reasons, the only treatment approaches that are acceptable are those that do not use substitution drugs (eg. methadone for opiate addiction). Experience gained in some countries using herbal preparations for addiction treatment seems to indicate that locally available and widely accepted treatment options may not only prove effective but may also result in considerable cost-savings.

The global spread of both heroin and the use of various stimulants has prompted experimentation with locally available natural products, mostly of herbal origin. New herbal concoctions are being designed, tested and proposed for the local treatment of drug addicts as cheap, affordable alternatives to expensive Western medications. Published and anecdotal reports indicate the extensive use of such medications in Asia (i.e. China, Thailand, Myanmar, Laos), designed to treat opium (heroin) addicts. Similar herbal preparations are marketed in various European countries for the symptomatic treatment of alcohol and nicotine-addicted individuals. The know-how for such herbal remedies usually comes from local systems of traditional medicine, e.g. Traditional Chinese Medicine, the Indian traditional systems of medicine, and from European ethnomedicine. The recipes for such herbal formulae have been developed by pharmaceutical companies, research

establishments or by learned individuals. The principal purposes of using such preparations include: precipitating a fast detoxification process; assisting the withdrawal process; reducing craving to maintain abstinence; and helping the body to recover both physically and mentally. Published, but insufficient evidence, suggests that some of these remedies may have potential value and may deserve further verification and development into marketed products.

Most current treatment programmes for substance abusers take into account only a small portion of the healing spectrum (e.g., psychological counselling, methadone, self-help, therapeutic community). There is a growing awareness of and concern to develop programmes for substance abusers using a holistic approach to deal with the mental, physical, emotional, and spiritual problems accompanying substance abuse. The current political climate in some countries is more accepting of the use of herbal medicine in the treatment of addiction and acknowledges the need for further international collaboration on herbal medicine assessment. However, there may be some problems in pursuing both experimentation and the use of herbal medicine in addiction:

- Lack of evidence; only small numbers of RCT trials have been carried out so far.
- Insurance companies do not pay for herbal compounds in most countries.
- No advertisement of herbs is offered by the industry.
- The real demand for herbal medicines from clients is unknown.

Although the importance of an evidence-based approach in assessing the effectiveness of herbal medicine is obvious, one might argue that herbal compounds should be taken as they are actually used by natives, without significantly altering their 'pharmaceutical' preparation. Otherwise, side effects which have never been reported by natives might occur.

At least in the western world, only peer-reviewed research published in learned journals is properly acknowledged and likely to attract research funds. A structured overview of the available Medline literature (1966 onwards) on herbs and plants as treatments for addictions has shown that the compounds most frequently identified by the search were Ibogaine and congeners; Ayahuasca; Kava; and Hypericum perforatum. At present, most of the scientific literature is made up of case reports or, at best, of open label studies. Only a few studies specific to addiction as a medical condition have been carried out, and most of them have either not been published at all, or have been published in non peer-reviewed journals. Hence, this information is not readily available to academic professionals. Furthermore, a difficulty often encountered by reviewers of ethnobotanical studies is the rather confusing and imprecise taxonomic specifications of herbs / plants / preparations that are reported by the researchers as having beneficial effects.

A further problem is the lack of a sufficient, reliable and steady supply of the index herbal compounds, not only for the required studies, but also for any anticipated future production. Without a reliable supply of raw material it proves difficult to justify costly research and development work. Environmental changes impose another threat to herbal medicine. A large number of plants species are currently in danger of disappearing which could also lead to the loss of traditional knowledge of their use in treatment and of their unique ingredients. The move of rural populations to cities is an additional threat. Endangered medicinal plants species include:

- Wild Asian ginseng
- Goldenseal
- Echinacea pallida
- Blue Cohosh

Most herbal compounds have not been used to treat drug addiction because this is a relatively new phenomenon in traditional cultures. Herbal medicine trials deserve the same scientific rigour as any other compound; and drug addicts need to be protected from the unscrupulous. When considering the development of herbal substances in the treatment of addiction it is therefore imperative that the following relevant questions are considered:

- What is the definition of a herbal medicine product?
- What does a herbal medicine compound offer to clinicians?
- Are these products going to be less or more expensive in comparison with established traditional medicines?
- What is the real acceptance of herbal medicine products within the general population?

The effectiveness of a herbal medicine should be formally assessed in randomised double-blind, double-dummy, placebo-controlled, parallel design, studies. For a brand new compound, before starting any RCT trials, phase 1 and 2 clinical studies should be carried out.

The challenges in carrying out trials with herbal medicine products were idenfied as follows:

i. Problem: what aspect of addiction is to be treated with herbal medicine products?
ii. Plants: which are the plants to be studied?
iii. People: which clients are be targeted? Ethical issues to be considered here
iv. Proposals: to be prepared to get appropriate funding.
v. Patent: at the end of any study, this may need to be be exploited.
vi. Production: publishing the results in international peer-reviewed scientific journals.

The following steps will be undertaken by the International Expert Group:

i. Publication of the present International Expert Group Report;
ii. Carrying out a 'data-gathering' exercise from countries not represented at the conference;
iii. Peer review examination of the available data on the use of herbal medicine in addictions; and
iv. Ranking of any putative herbal medicine compound in 3 groups:
    a. Not having an immediate interest for further studies
    b. Having an interest, but phase 1 and 2 trials need to be carried out before an RCT is being considered
    c. Products that may be promoted to go through a randomised, double-blind, double-dummy, placebo-controlled, parallel (or cross-over) design in humans.

The possibility of publication of a monograph by a commercial publisher will be considered.

Experts from China, Brazil and Mexico suggested further meetings of the International Expert Group should be held in these countries, where traditional herbal medicine has been widely used. There was a further suggestion for a meeting to take place in the UK. The importance of the continuation of the work of the Group was highlighted to gather and share information in this field.

10.0 Glossary

AchE:	acetylcholinesterase
ASW:	Aswaganda
AMPA receptor:	-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid AMPA receptor (AMPAR) is a non-NMDA-type ionotropic transmembrane receptor for glutamate
BD:	two times a day
Bmax:	maximum specific binding to receptors
BuchE:	butynilcholinesterase
CAM:	complementary and alternative medicines
CAPES:	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - a Brazilian information system
CEBRID:	Centro Brasileiro de Informações sobre Drogas Psicotrópicas (Brazilian Centre for Information on Psychotropic Drugs)
CMT:	acronym for a compound which is a mixture of 27 different ingredients and whose composition has not been made public by the Thai professionals.
CRSS:	Ghanese University Centre for Research and Scientific Studies
CYP450:	cytochrome P 450
DA:	dopamine
DSM-IV:	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, American Psychiatric Association, 1994.
EU:	European Union
GPs:	General Practitioners
ICD-10:	International Classification of Diseases, 10th edition, World Health Organization
IMEPLAN:	Mexican Institute for the Study of Medicinal Plants
LTP:	long-term potentiation
M1;	M2 receptors: muscarinic 1 and 2
Medline:	Online database of life sciences and biomedical bibliographic information compiled by the U.S. National Library of Medicine.
NIDA:	National Institute on Drug Abuse
NIDD:	Chinese National Institute of Drug Dependence
NMDA:	N-Methyl-D-Aspartate
NUPAUB-USP:	Support Unit for Research on Human Populations in Brazilian
OTC:	over-the-counter
PubMed:	Produced by the U.S. National Library of Medicine, an online database of scientific/biomedical literature.
RCT:	randomized controlled trial
SSRIs:	selective serotonin reuptake inhibitors
TCM:	Traditional Chinese Medicine
TDS:	three times a day
5-HT; 5HT2:	serotonin; serotonin2
UK:	United Kingdom
UN:	United Nations
UNDP:	United Nations Development Programme
UNOPS:	United Nations Offices for Project Services
UNESCO:	United Nations Educational, Scientific and Cultural Organization
WHO:	World Health Organization

11.0 References

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